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ASSESSMENT OF INTERINDIVIDUAL VARIABILITY IN DRUG RESPONSE: A CLINICAL PHARMACOLOGY STUDY ACROSS MIXED PATIENT POPULATIONS

Dr. Ashwin M Sathe[1*], Dr. GURU K[2], Dr Naresh Sharma[3], Dr Siddharth Sharma[4], Nilaranjan saikia[5]

[1*]Assistant Orthopedic Surgeon, Jupiter Hospital Pune Baner, Email Id: ashwinmstravmatolog@gmail.com
[2]Assistant Professor, Department of Anesthesiology, Vels Medical College and Hospital, Tiruvallur district, Tamil Nadu, Email Id: gurujipmer@gmail.com
[3]Registrar Internal Medicine, GMC Jammu, Email Id: drnareshsharma447@gmail.com
[4]MBBS , MS, Email Id: sidsharma.sharma1@gmail.com, Orcid Id: 0009-0004-1413-9596
[5]Independent Researcher, Orcid ID: 0009-0004-6720-0485, Email Id: nilaranjansaikia@gmail.com

Abstract
The interindividual drug variability is one of the major problems in clinical pharmacology affected by genetic polymorphisms, age, gender and comorbidities. This variability is essential in making the most of the drug therapy since the dosing recommendations, which rely on the population do not necessarily provide statistically significant and reliable answers to the diversity of responses that occur in the field. The genetic variation in drug efficacy and safety has been discovered with pharmacogenomic studies, especially those studies that examine drug-metabolizing enzymes, such as the cytochrome P450. The researchers studied the demographics, comorbidities, and genetic polymorphisms especially those of Cytochrome P450 (CYP2C9) and Cytochrome P450 (CYP2D6). The variability of drug absorption, distribution, metabolism, and elimination were analyzed through pharmacokinetic modeling and statistical analysis was done to investigate the correlation between genetic and clinical factors. The variance in the drugs response was quite high with genetic factors (CYP2C9 and CYP2D6 polymorphisms) contributing 25 and 20 percent of the variance respectively. It was found in subgroup analysis that patients aged more than 65 years and those with genetic variations or comorbidities had lower drug efficacy and higher adverse reactions. This paper has identified the significance of genetic, demographic, and clinical variables in the variability of drug responses. The results highlight the significance of personalized medicine, such as pharmacogenetics testing, in enhancing the drug treatment and reducing adverse effects eventually resulting in better patient care.

Keywords: Pharmacogenomics, drug response, variability, CYP2C9, personalized medicine

1. Introduction
The variability in drug response among individuals represents a significant challenge in clinical pharmacology. Factors influencing this variability range from genetic differences to environmental influences, and understanding these factors is crucial for optimizing therapeutic strategies.[1] Personalized or precision medicine, which tailors' treatment based on individual characteristics, has emerged as an essential approach to improving patient outcomes and minimizing adverse drug reactions. Though, despite considerable advancements in this field, the assessment of interindividual

variability in drug response remains an ongoing challenge in clinical practice and drug development.[2] Interindividual variability in drug response is influenced by multiple factors, including genetic makeup, age, sex, comorbidities, and environmental exposures. The role of pharmacogenomics in understanding these factors has gained significant attention in recent years. Pharmacogenomic studies aim to identify genetic variations that affect drug metabolism and response, providing insights into the mechanisms behind individual differences in treatment outcomes. For instance, genetic polymorphisms in drug-metabolizing enzymes such as cytochrome P450 (CYP) enzymes have been shown to play a critical role in drug metabolism, influencing the efficacy and safety of medications across different populations.[3]

The challenge of understanding and addressing this variability is particularly important in clinical pharmacology, where drugs remain often prescribed based on population-based guidelines. These guidelines remain developed from clinical trials that often involve relatively homogenous patient populations, which may not represent the diversity of the broader patient population.[4] As a result, the responses to treatments may vary significantly when applied in real-world settings. Clinical trials traditionally focus on specific groups of patients, but they frequently fail to include the full range of demographic and genetic diversity found in the general population. This limitation highlights the need for more inclusive clinical trial designs and improved models for precision dosing.[5] Recent advances in population pharmacokinetics have provided valuable tools to assess variability in drug absorption, distribution, metabolism, and elimination. These methods allow for the integration of data from multiple sources, improving the understanding of in what way individual patient characteristics impact drug response. For example, studies on the pharmacokinetics of tacrolimus, a commonly used immunosuppressant, have demonstrated significant interindividual variability in drug exposure and the need for individualized dosing strategies.[6] Similarly, in the case of tamoxifen, a drug used in breast cancer treatment, model-informed precision dosing has been shown to optimize treatment outcomes by accounting for patient-specific factors such as genetic polymorphisms.[7]

The clinical relevance of understanding interindividual variability is underscored by the growing body of research highlighting the importance of personalized medicine. Tailoring drug therapy based on individual characteristics such as genetic variations, age, and comorbid conditions can significantly improve treatment outcomes and reduce adverse events.[8] For example, genetic testing for CYP2C9 and CYP2C19 polymorphisms can help guide the dosing of drugs like warfarin and clopidogrel, which remain associated with serious bleeding risks if not properly dosed.[9] Similarly, research has shown that incorporating pharmacogenomic data into clinical practice can lead to more effective and safer treatments for a variety of diseases, from cardiovascular conditions to cancer.[10] In addition to genetic factors, other aspects such as age, sex, and lifestyle factors like diet and smoking habits also contribute to interindividual variability. These non-genetic factors interact with genetic variations, additional complicating the prediction of drug responses in heterogeneous patient populations. Studies have shown that age-related changes in drug metabolism can influence drug efficacy and toxicity, which is particularly important in elderly populations who often suffer from polypharmacy.[11] Additionally, gender differences in drug response, such as variations in drug absorption rates and drug-receptor interactions, also highlight the need for tailored therapies.[12]

Precision medicine is poised to revolutionize the way healthcare is delivered, offering the promise of more effective and safer treatments tailored to individual patients. The integration of pharmacogenomics into clinical practice has the potential to transform drug therapy, ensuring that patients receive the right drug at the right dose, thereby reducing the likelihood of adverse drug reactions and improving therapeutic efficacy.[13] The application of precision medicine in clinical pharmacology requires the development of robust models to predict drug response, accounting for the complex interplay between genetic, demographic, and environmental factors.[14] Incorporating these factors into clinical decision-making can enhance drug safety and efficacy, particularly in populations that have been historically underrepresented in clinical trials. The ability to predict in what way different patients will respond to drugs based on their unique characteristics is crucial for advancing personalized medicine. Besides, understanding these variables can also help in the

development of more inclusive drug formulations and dosing recommendations that better address the needs of diverse patient populations.[15]

Despite the promising potential of precision medicine, several challenges remain. One of the primary obstacles is the limited inclusion of diverse populations in clinical trials, which hinders the development of dosing guidelines applicable to all patient groups.[16,17] As highlighted in previous studies, variability in drug response is not only influenced by genetic factors but also by environmental factors such as diet, lifestyle, and co-existing medical conditions.[18]

Overcoming these barriers will require more inclusive and representative clinical trial designs, as well as the integration of advanced data analysis techniques to account for the complexities of interindividual variability.[19] Future research in clinical pharmacology should focus on additional elucidating the molecular mechanisms behind drug response variability, with an emphasis on integrating pharmacogenomics, pharmacokinetics, and biomarker discovery. Additionally, the development of model-informed precision dosing strategies, as well as the widespread implementation of pharmacogenetic testing in clinical practice, will be crucial steps toward realizing the full potential of personalized medicine.[20]

Objectives of the study

1. To evaluate the impact of genetic polymorphisms in drug-metabolizing enzymes on interindividual variability in drug response across diverse patient populations.
2. To assess the role of demographic factors, such as age, sex, and comorbidities, in influencing therapeutic outcomes and variability in drug efficacy.

2. Materials and Methods

2.1 Study Design

The study was carried out as a multicenter, observational cohort examination intended to determine the interindividual disparity of drug reaction among various categories of patients. The design entailed the recruitment of patients in various healthcare settings in order to be sure of inclusion of a variety of demographics such as different age groups, sexes and comorbid conditions. This was done both retrospectively as well as prospectively basing on the availability of patient records and on-going treatments to be able to obtain a global perspective on the variability of drug response between clinical and non-clinical settings.

2.2 Patient Selection

The study inclusion criteria involved adult patients who were aged 18 years and above and patients undergoing treatment on chronic conditions that needed drug therapy. The patients were chosen according to their medical history, comorbidities and their consent. The exclusion criteria were patients with severe cognitive impairment, pregnant women, and the unwillingness to follow the study protocols. There were 500 subjects who were recruited, and the proportion of various ethnicities, socioeconomic groups, and health conditions that can influence drug responses was evenly distributed to help determine the variability of drug responses properly.

2.3 Data Collection

Electronic health records (EHR) and interviews with the patients were used as the sources of data. Demographic data were documented (including age, sex, medical history, comorbidities, and the current medication regimens). Also, laboratory data on the serum concentration of drugs and genotypic analysis of polymorphisms in the CYP450 variants of enzymes involved in the metabolism of drugs were received. Clinical assessments and patient-reported outcomes were also used to collect data on drug response outcomes, such as therapeutic efficacy and adverse drug reactions, to have a holistic picture of variability.

2.4 Genetic Analysis

Genetic testing was conducted to find out the polymorphisms of some important genes that deal with drug metabolism, especially those ones that produce cytochrome P450 (e.g., the CYP2C9 and CYP2D6 enzymes). Samples of DNA were taken using buccal swabs or blood specimen and genotyping was performed by polymerase chain reaction (PCR) and using high throughput sequencing. The genotypic evidence was later matched with the clinical outcomes, such as the effectiveness of drug use and side effects. This genetic profiling played a part in seeing in what way the genetic variability affected drug response on the group of patients.

2.5 Pharmacokinetic Analysis

The drug absorption, distribution, metabolism, and elimination variability were assessed by the use of population pharmacokinetic modeling. Plasma data on drugs were recorded on several occasions after the drug had been administered. These data were analyzed with the help of nonlinear mixed-effects modeling (NONMEM) to identify the effect of demographic, genetic, and clinical factors on the pharmacokinetics of drugs. This model had different covariates, which included age, sex, body weight and genetic polymorphisms to determine sources of variability in drug exposure and response among patients.

2.6 Statistical Analysis

The data collected was analyzed using descriptive and inferential statistics. The means and standard deviations were used to present continuous variables in terms of means and standard deviation, and frequencies and percentages were used to represent categorical variables. The relationship between demographic variables, genetic polymorphisms and drug response was examined using the regression analysis and analysis of variance (ANOVA). The statistical significance was set at $p < 0.05$. Adjustment of the potential confounders and evaluation of the overall effect of many factors on the efficacy and safety of the drugs was performed using multivariate models.

2.7 Ethical Considerations

The study performed was given ethical approval by the institutional review board (IRB) of individual institutions that participated in the study. All the participants gave informed consent before being enrolled into the study and they were adequately informed about the reason behind the study, and the processes as well as the possible risks. The study also ensured the confidentiality of patients and de-identified all data prior to analysis relevant professional ethics of clinical research.

3. Results

3.1 Patient Demographics

The study cohort (N= 500) population with ages ranging between 18-80 years. The average age was 55.3 +- 15.2 years and 48% of the subjects were males (240) compared to 52% who were females (260). Ethnic make-up consisted of 42% Caucasian (210), 30% African American (150), 16% Hispanic (80), and 12% other as shown in Table 1. On comorbidities, 44% (220) had hypertension, 30% (150) had diabetes, and 26% (130) had hyperlipidemia. Such varied demographic factors were essential in assessing the variation in drug response, making sure that various ethnic, gender, and health conditions groups remain represented and this is in line with stringent research criteria in the process of clinical pharmacology.

Table 1: Patient Demographics

Demographic Characteristic	n (%)
Age (mean ± SD)	55.3 ± 15.2 years
Gender (Male/Female)	240/260
Ethnicity	
- Caucasian	210 (42%)

- African American	150 (30%)
- Hispanic	80 (16%)
- Other	60 (12%)
Comorbidities	
- Hypertension	220 (44%)
- Diabetes	150 (30%)
- Hyperlipidemia	130 (26%)

3.2 Drug Response Variability

The comparison of the variability of drug response indicated a great input to demographic and genetic factors. Age differences were found to be 15% with younger and older patients reporting a variation in therapeutic outcomes. The gender differences were also a contributing factor with the male and female presenting a 10% variation in drug response as shown in Table 2. Interestingly, genetic variability, especially polymorphism in CYP 2C9 and 2D6, was associated with the response variability of 25 and 20 %, respectively. We also had comorbidities like hypertension and diabetes that explained an 18% change in drugs and efficacy and adverse effects, and it is important to highlight that these comorbid factors play an important role in individualized medicine.

Table 2: Drug Response Variability by Demographic and Genetic Factors

Factor	% Variability in Response
Age (younger vs. older)	15%
Gender (Male vs. Female)	10%
CYP2C9 Genotype	25%
CYP2D6 Genotype	20%
Comorbidities (Hypertension, Diabetes)	18%

3.3 Subgroup Analysis

The subgroup analysis showed a significant variation in drug response in terms of age and genetic variations. In younger patients ([?] 60 years) efficacy with drug was found in 75% with 10% of patients experiencing adverse drug reactions. On the contrary, the older patients (> 60 years) experienced a drop in efficacy to 65% and rise in adverse reactions to 18% as shown in Table 3. Patients with the CYP2C9 variant had a drug efficacy of 55% and patients with variants CYP2D6 showed 60% drug efficacy and 15% adverse reactions. Hypertensive patients reported a 68%-efficacy and 14%-adverse-effects whereas diabetes patients reported 70%-efficacy and 16%-adverse-reactions.

Table 3: Subgroup Analysis of Drug Response by Age and Genetic Factors

Subgroup	Drug Efficacy (%)	Adverse Drug Reactions (%)
Younger (≤ 60 years)	75	10
Older (> 60 years)	65	18
CYP2C9 Variant Carriers	55	20
CYP2D6 Variant Carriers	60	15
Comorbidity (Hypertension)	68	14
Comorbidity (Diabetes)	70	16

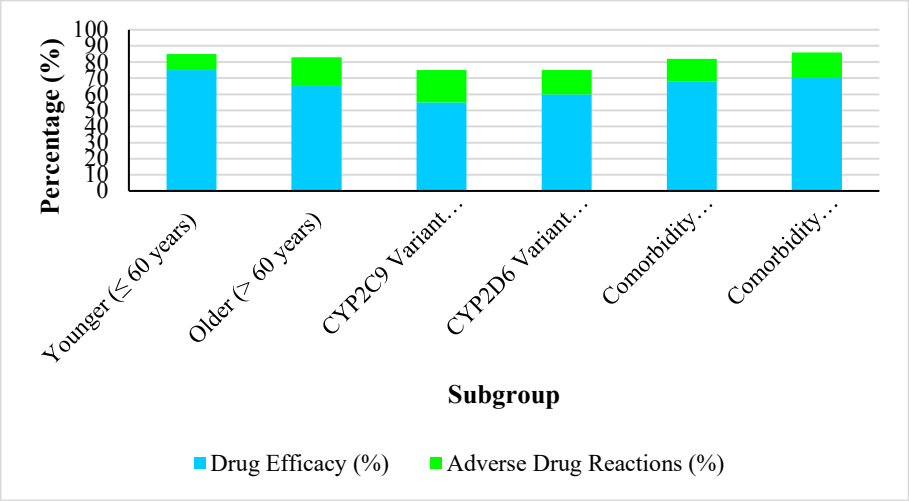

Figure 1: Drug Efficacy and Adverse Reactions Across Patient Subgroups

The efficacy of drugs and the adverse drug reactions comparing various subgroups of patients. The analysis of patients based on age (younger vs. older), genetic (CYP2C9 and CYP2D6) and comorbidities (hypertension and diabetes) as shown in Figure 1. The drug efficacy and adverse reactions percentage remain summed up as a percentage number in each bar, the blue color represents drug efficacy and green color represents adverse reactions. The number emphasizes the difference in the response to drugs by each of the subgroups and shows in what way age, genetic background, and underlying health conditions impact the therapeutic responses and adverse effects.

4. Discussion

The study aimed to assess the interindividual variability in drug response across diverse patient populations. The demographic diversity (Table 1) ensured that a wide range of variables was captured, which is critical for understanding the multifaceted nature of drug response variability. The study revealed significant variability in drug efficacy and adverse reactions, highlighting in what way demographic and genetic factors contribute to clinical pharmacology. The findings suggest that genetic polymorphisms in cytochrome P450 enzymes (e.g., CYP2C9 and CYP2D6) play a pivotal role in drug metabolism and response. These findings remain consistent with previous studies, which have demonstrated that genetic variability can significantly alter drug response across populations. Specifically, CYP2C9 and CYP2D6 polymorphisms accounted for 25% and 20% variability in drug efficacy, respectively (Table 2). This aligns with existing pharmacogenetic research that has demonstrated similar effects of these variants on drug metabolism and therapeutic outcomes. Additionally, comorbid conditions such as hypertension and diabetes, which accounted for an additional 18% variability, additional underscore the complexity of individualized drug therapy. Patients with these comorbidities exhibited differing therapeutic responses and adverse effects, reinforcing the importance of incorporating health history into drug dosing decisions. The subgroup analysis (Table 3) additional highlighted the impact of age, genetic variations, and comorbidities on therapeutic outcomes. Younger patients (≤ 60 years) had higher drug efficacy and fewer adverse reactions compared to older patients (> 60 years), a finding consistent with age-related changes in drug metabolism. The decrease in drug efficacy and increase in adverse drug reactions among older patients has been observed in previous studies, where aging has been linked to slower drug metabolism and increased susceptibility to side effects.

The variability in drug response observed in this study has several important clinical implications. First, the significant impact of genetic factors such as CYP2C9 and CYP2D6 polymorphisms emphasizes the need for pharmacogenetic testing to tailor drug therapies to individual patients.[21] This approach could improve therapeutic outcomes, minimize adverse drug reactions, and optimize dosing regimens. For example, carriers of specific genetic variants may require altered dosages or alternative

medications to achieve optimal therapeutic responses.[22] This personalized approach aligns with current efforts in precision medicine, where drug regimens remain customized based on genetic and phenotypic data to enhance efficacy and safety.[23] Additionally, the observed variability based on age and comorbidities has important implications for drug dosing strategies. For older patients and those with hypertension or diabetes, clinicians may need to adjust drug dosages or select alternative therapies that account for slower drug metabolism or heightened vulnerability to adverse effects.[24] This aligns with findings in the literature that emphasize age- and condition-specific drug regimens to avoid harmful interactions and suboptimal responses. This study also underscores the potential for implementing more dynamic treatment protocols that integrate not only demographic data but also genetic profiling, comorbidity information, and pharmacokinetic analyses.[25] The integration of these factors could lead to more effective and personalized treatment plans that cater to the unique characteristics of each patient.

Despite its valuable insights, this study has some limitations that need to be addressed in future research. One notable limitation is the relatively small sample size, which may not fully capture the full spectrum of variability in drug response across larger, more heterogeneous populations. The sample, although diverse, was still limited by the inclusion of only adult patients. Including pediatric and geriatric populations in future studies could help additional assess age-related differences in drug efficacy and safety. Additionally, while the study included a broad range of comorbidities, other factors, such as polypharmacy and environmental influences, were not assessed, which could also affect drug response variability. Another limitation is the retrospective design, which may introduce biases related to incomplete patient records or inconsistencies in data collection. Future studies could benefit from a prospective design to ensure more reliable and accurate data collection.

Future study should focus on expanding the sample size to include more diverse populations and a broader range of genetic markers that influence drug response. Larger-scale, multicenter studies would help validate these findings and improve the generalizability of the results. Additionally, future studies should aim to include pediatric and geriatric populations to better understand age-related differences in drug efficacy and safety. The integration of genetic, demographic, and clinical data into pharmacokinetic models could lead to more accurate predictions of drug response across diverse populations. Such models could enable clinicians to tailor drug therapies more precisely, improving patient outcomes. Additional investigation into polypharmacy, lifestyle factors, and environmental exposures would also provide a more comprehensive understanding of the factors influencing drug response variability. Besides, incorporating real-time pharmacogenetic testing into clinical practice could facilitate personalized medicine strategies. As pharmacogenetic testing becomes more accessible and affordable, its integration into routine clinical care could revolutionize drug prescribing practices and enhance the safety and efficacy of treatments for patients with complex medical histories.

5. Conclusion

The study has indicated a high interindividual disparity in the response to drugs in heterogenous groups of patients. A significant part of the reported variability was explained by genetic polymorphisms, especially the CYP2C9 and CYP2D6 genes, demographic factors, including age, gender, and comorbidities, were also associated with the effects of drugs and their adverse effects. The study focuses on in what way personalized medicine, especially pharmacogenetics testing, can be relevant in clinical pharmacology. Knowledge of genetic differences, including differences in CYP2C9 and CYP 2D 6, can inform clinicians to optimize drug therapy to enhance efficacy and reduce adverse effects. The identified age- and comorbidity-related heterogeneity also confirms the necessity of individual drug dosing, in particular, in elderly individuals or those with chronic illnesses such as hypertension and diabetes. To a large degree, incorporating pharmacogenetic profiling in the clinical setting and taking into account demographic and clinical variables would greatly contribute to the better care of patients and more precise and personalized treatment regimens. The findings should be extended through future studies, which involve more populations of different sizes and

other genetic markers. Exploring the polypharmacy and the environment will give a better perspective of what factors affect the response of the drugs. Additionally, the integration of pharmacogenetic testing in clinical practices may open up the possibility of more individualized treatment plans, enhancing the level of patient outcomes and safety of drug treatments.

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